Cells decide when to divide based on their internal clocks

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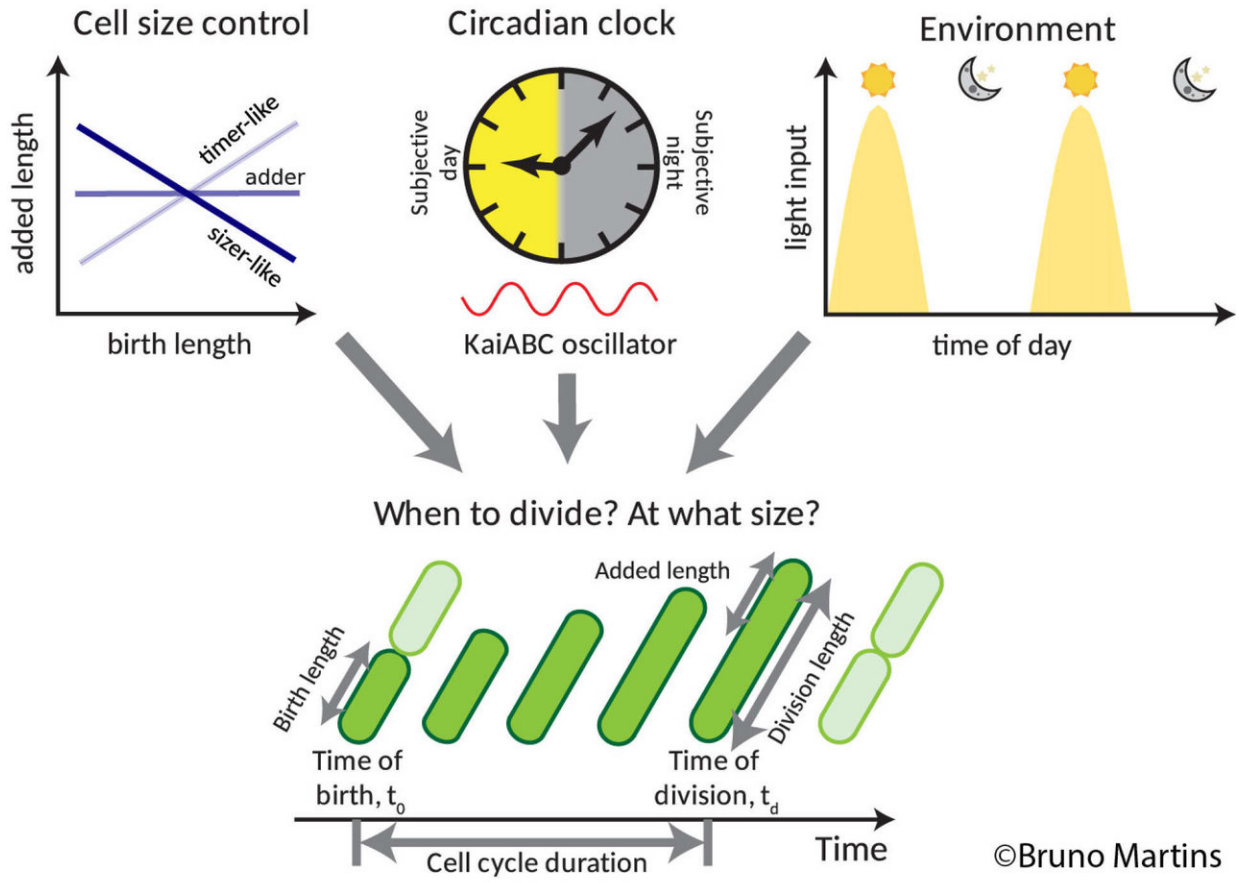

Cell size, circadian clock and environment all influence when cells divide.
Credit: Imperial College London

Cells replicate by dividing, but scientists still don't know exactly how

they decide when to split. Deciding the right time and the right size to divide is critical for cells – if something goes wrong it can have a big impact, such as with cancer, which is basically a disease of uncontrolled cell division.

Several factors are thought to play a role in a cell's decision to divide, including the size of the cell, the time of day, and cues from the environment, such as the amount of light.

Now, in a study with single-celled organisms called cyanobacteria, scientists from the University of Cambridge and Imperial College London have shown how the time of day affects when cells divide, and at what size.

Cells, and whole organisms, respond to the time of day in a pattern according to their internal 'circadian clock'. For example, in mammals the circadian clock controls cell regeneration and the release of hormones, and in plants it controls flower opening and photosynthesis.

Published in the journal *Proceedings of the National Academy of Sciences*, the new study by scientists at the Sainsbury Laboratory Cambridge University (SLCU) and the Department of Mathematics at Imperial College London shows that the circadian clock continuously influences cyanobacteria cell division throughout the day and night.

This finding rewrites the most recent understanding that the clock was only acting as an 'on/off' switch to cell division – enabling cells to replicate only at set times.

The team designed a set of experiments with colonies of cyanobacteria to pick apart the influence of time of day, size of cell, and the presence of light on cell division.

First, they observed division rates for cyanobacteria altered to lack circadian clocks, as well as rates of unaltered cells under constant light conditions.

Using the division patterns from these experiments, and what was thought to influence them, Imperial mathematicians and collaborators then designed models to predict what would happen if the light changed over the course of future experiments.

In the subsequent experiments, the team found that rather than the circadian clock acting like an on/off switch or 'gate', forbidding cell division at certain times, it acts to fine tune the process by decreasing division at certain times and accelerating it at others.

What they found matched the second set of experiments well, meaning their models successfully described the mechanisms at play.

Dr. Philipp Thomas, from the Department of Mathematics at Imperial, said: "Instead of acting as a strict gate for cell division, the circadian clock constantly influences the division rate throughout the day. Unpicking the complex interactions between cell size, clock and environment was only possible through the careful combination of experiments and iterative models that determined the contribution of the factors at play."

The timing pattern identified led to two sub-populations of cyanobacteria that divided at different sizes, depending on what time cells where born.

Lead author of the study, Dr. Bruno Martins from the University of Cambridge, said: "Cells born in the early part of the day grow to a smaller size before dividing again, because they seem to be in a 'rush' to divide before the end of the day. In contrast, cells born later in the day

are in less of a 'rush', and therefore they grow to a bigger size, and avoid dividing in the period that normally corresponds to darkness at night."

The team will next use their experimental results and the models developed to explain them to look at what molecules and genes are involved in this process and to explore its evolutionary function.

More information: Bruno M. C. Martins et al. Cell size control driven by the circadian clock and environment in cyanobacteria, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1811309115

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